The Examiner stated:

> Kruse et al. teaches production of the muteins of IL-4 R121D, K123D, Y124D, S125D in *E.coli*. They measured receptor affinities of the variants are during competitive radioligand binding to Raji cells (Table1). However, Kruse et al. does not discuss the altered specificity of the muteins/variants.
>
> Duschl discloses the mutations in the IL-4 signaling site prevent association of γc, but not binding to IL-4Rα using conventional binding studies. This demonstrates that intact signaling site of IL-4 is required to recruit γc into the receptor complex (see abstract). Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made to analyze the muteins of the instant inventions as disclosed in Kruse et al. and Duschl et al. to study the change in affinity and specificity to various subunits, because Kruse et al. teaches that identifying the affinity and specificity will allow for rational design of high affinity IL-4 antagonist. Therefore, the instant invention is obvious over Kruse et al. (1993) in view of Duschl (1995).

As amended and claimed, the present invention relates to hIL-4 muteins having a reduced affinity and/or an altered specificity to the γ subunit of the IL-4 receptor and/or HIL-13 Rα subunit of the hIL-4 receptor, wherein one or more amino acids at positions 7, 11, 12, or 15 have been substituted with another amino acid (claim 9) and in addition, one or more amino acids substitutions at positions 121, 123, 124, or 125 (claim 10).

Kruse et al., does not teach or suggest the amino acids substitutions at positions 7, 11, 12, or 15; nor the combination of amino acids substitutions at positions 7, 11, 12, or 15 and substitutions at positions 121, 123, 124, or 125. In addition, Kruse et al. does not teach or suggest IL-4 muteins that have a reduced affinity and/or an altered specificity for the γ subunit. Kruse et al., states that IL-4 provides functionally distinct sites for interactions with receptor proteins, that is a "signalling site" and a "binding site" for IL-$4R_{ex}$ (the α subunit of the IL-4 receptor) (*see, eg.,* page 5125). In fact, Kruse et al., states that the "signalling site" is located in helix D and the "binding site" for IL-$4R_{ex}$ (the α subunit of the IL-4 receptor) is located in helices A and C. Thus, one skilled in the art would not be motivated to substitute amino acids at positions 7, 11, 12, or 15, located within the helix A, with the reasonable expectation of success, that is, producing an IL-4 mutein with a reduced affinity and/or an altered specificity for the γ subunit because helix A appears to be associated with the "binding site" for IL-$4R_{ex}$ (the α subunit of the IL-4 receptor).

The deficiencies of Kruse et al., are not remedied by Duschl. Duschl does not teach or suggest the amino acids substitutions at positions 7, 11, 12, or 15; nor the combination of amino acids substitutions at positions 7, 11, 12, or 15 and substitutions at positions 121, 123, 124, or 125. Similar to Kruse et al., Duschl states that helices A and C are associated with receptor binding. Furthermore, Duschl states that mutations of residues in helices A and C of IL-4 result in a loss of receptor binding (*see, eg.,*

page 305). That is, these IL-4 mutants of helices A and C fail to bind to the α subunit of the IL-4 receptor. Thus, one skilled in the art would not be motivated to substitute amino acids at positions 7, 11, 12, or 15, located within the helix A, with the reasonable expectation of success, that is, producing an IL-4 mutein with a reduced affinity and/or an altered specificity for the γ subunit.

Since the combination of references does not teach every element of the claimed invention, these references cannot be combined to support a rejection of the claims under U.S.C. § 103(a). MPEP § 2143.

It is therefore respectfully submitted that Kruse et al., either singly or in combination with Duschl fail to teach or suggest the IL-4 muteins as presently claimed, and that the current invention is novel and nonobvious in view of the prior art references. For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the present rejection.

CONCLUSION

For the foregoing reasons, Applicants submit that the claim is in condition for allowance and Applicants respectfully request reexamination of the present application, reconsideration and withdrawal of the present rejections and entry of the amendments. Should there be any further matter requiring consideration, Examiner Seharaseyon is invited to contact the undersigned counsel.

If there are any further fees due in connection with the filing of the present reply, please charge the fees to undersigned's Deposit Account No. 13-3372. If a fee is required for an extension of time not accounted for, such an extension is requested and the fee should also be charged to undersigned's deposit account.

Respectfully submitted,

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Susan M. Pellegrino
Reg. No. 48,972

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Telephone: (203) 812-6450
Facsimile: (203) 812-6459
E-mail: susan.pellegrino.b@bayer.com

Amendment to Specification for Attorney Docket Number LeA 32 545

Amendment to Title:

Muteins of Interleukin 4 [showing low-affinity and short-term interaction with the common γ chain]

New Claims for Attorney Docket Number LeA 32 545

E2

10. (New) An hIL-4 mutein according to claim 9, wherein one or more amino acids at position 121, 123, 124, or 125 have been substituted with another naturally occurring amino acid.

Amended Claims for Attorney Docket Number LeA 32 545

9. (Amended) An hIL-4 mutein having a reduced affinity and/or an altered specificity to the γ subunit of the IL-4 receptor and/or HIL-13 R α subunit of the hIL-4 receptor, wherein one or more amino acids at positions 7, 11, 12, or 15 have been substituted with another naturally occurring amino acid.

Amendments to the Claims (Attorney Docket No. Le A 32 545)
Version with Markings to Show Changes to Specification

9. (Amended) An hIL-4 mutein having a reduced affinity and/or an altered specificity to the γ subunit of the IL-4 receptor and/or HIL-13 R α subunit of the hIL-4 receptor, wherein one or more amino acids at positions 7, 11, 12, or 15[, 121, 123, 124, or 125] have been substituted with another naturally occurring amino acid.